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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,282	06/27/2007	Michele Reboud-Ravaux	045636-5084	2668

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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1643

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/583,282	Applicant(s) REBOUD-RAVAUX ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
4a) Of the above claim(s) 4-6 and 12-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 7-11 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>6/16/06</u> . | 6) <input type="checkbox"/> Other: ____. |

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DETAILED ACTION

Claims 1-18 are pending and examined on the merits.

Claim Objections

Claims 4-6, 12-18 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot serve as the basis for another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 4-6, 12-18 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is vague and indefinite in the recitation of “preferably 4 to 8 amino acids” and “even more preferably 6 amino acids”. It is unclear how the preferred embodiments influence the scope of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

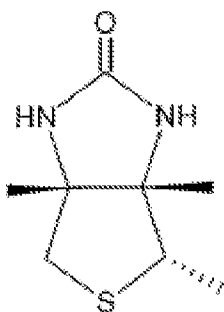
Claims 1-3, 7-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a molecule of the general formula I, wherein $X_0=0$, does not reasonably provide enablement for a molecule of the general formula I, wherein $X_0=1$. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re wands, 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir. 1988)..

An index of X0=1 requires the fused heterocycle structure indicated in formula II



This structure is related to biotin with the exception of two methyl groups attached to the bridging carbons. It is well known in the field of organic chemistry that an indication of a bond without a further substituent is indicative of a methyl group. Neither the specification, nor the prior art disclose such an analog of biotin, nor how to synthesize such an analog. The contemplation of the instant formula II requiring two methyl groups attached to the bridging atoms of a biotin heterocycle is not commensurate with the requirements of 112, first paragraph because the chemical synthesis art is unpredictable with respect to multifunctional molecules. The art teaches that presence of differing functional groups, heteroatoms and three dimensional configurations such as those required for formula II require different considerations as to protecting groups, and reactivity manifest in different synthetic strategies (Sierra and de la Torre, *Angewandte Chemie*, 2000, Vol. 39, pp. 1538-1559, especially pages 1544-1546, "Troublesome Protecting Groups"). Chemical structure heterogeneity including the presence of different heteroatoms on different three dimensional structures can radically alter the reactivity of any other atom within a molecule through inductive effects (page 1545, second column, lines 2-6 of

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the second full paragraph and lines 4-7 of the third full paragraph, resonance effects, acidity, basicity and steric hindrance (page 1552-1554), strain (page 1554-1557) or transition state crowding (page 1545, second column, second full paragraph, lines 2-6., page 1546, second column, first full paragraph) and therefore can radically influence the reactivity with any given reagent contacted thereto. Sierra and de la Torre teach that a well-testing transformation can fail for complex reasons (Sierra and de la Torre, *ibid*, page 1540, first column, lines 9-11, page 1541, first column, lines 33-37, under the heading “Working Models that do not Work”, page 1542, first column, lines 15-17, even when supported by molecular mechanics calculations (page 1542, first column, lines 6-9) and what is seen as an innocuous alteration can cause a failure in a synthetic step (page 1542, second column, lines 9-12). Sierra and de la Torre teach that the presence of remote substitutions has unexpected influence over a chemical step (pages 1546-1548, under the heading “The Unexpected Influence of Remote Substituents”) Sierra and de la Torre state that “As the complexity of intermediates increases, the number of variables involved in a simple transformation grow exponentially making predictions about the outcome of any given synthetic step on a highly functionalized intermediate, unreliable (page 1548, second column, lines 5-8 of the second full paragraph, page 1550, second column, lines 1-9 under the heading “The Trivial Functional Group Transformation”). Sierra and de la Torre conclude that the lack of predictability in so many cases and the very empirical nature of synthetic organic chemistry implies that the science is not fully developed (page 1548, second column, lines 13-16 of the second full paragraph). Sierra and de la Torre state that alternate routes can then be devised which circumvent a failed transformation (page 1548, second column, lines 10-13 of the second full paragraph), however, the sum total effort of designing and redesigning represents undue experimentation to one of skill in the art, exemplified by Sierra and de la Torre as “the amount of effort devoted to simple transformations is still quite enormous” (page 1557, first column, lines 15-18). Thus it is concluded that due to the unpredictability of the art that contemplation of a synthetic target compound, such as that of Formula II, is not commensurate with a disclosure of how to make said compound.

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The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Reboud-Ravaux ('Proteasome Inhibitors', In: Progress in Molecular and Subcellular Biology, 2002, Vol. 29, pp. 109-125).

Claim 1 is drawn in part to a molecule of general formula $(X0)_{x0}-(X1)_{x1}-(X2)_{x2}-(X3)_{x3}-(X4)_{x4}-(X5)_{x5}-(X6)_{x6}-(X7)_{x7}-(X8)_{x8}-(X9)_{x9}$, wherein $x0=0$, X1 and X3 represent natural or synthetic amino acids having hydroxyl side chains, X2 represents natural or synthetic amino acids having alkyl side chains, X4 represents natural or synthetic amino acids having aromatic side chains, $x5=0$, X6 represents a natural or synthetic amino acid in the D or L configuration which can be phenylalanine, leucine or isoleucine, X7 represents a natural or synthetic amino acid in the D or L configuration which can be leucine or valine, X8 represents a natural or synthetic amino acid in the D or L configuration which can be valine or isoleucine, and X9 represents a natural or synthetic amino acid in the D or L configuration which can be serine; wherein the bond between two successive amino acids can be a peptide bond; the amino acids being capable of comprising a modification of the alpha carbon. Claim 2 embodies the molecule of claim 1 characterized in that at least one of the integers of X0 through X9 is equal to 1, X2 is chosen from a group consisting of valine, leucine and isoleucine and X4 is chosen from a group consisting of phenylalanine. Claim 3 embodies the molecule of claim 1 or claim 2 wherein said molecule comprises 4 amino acids

Reboud-Ravaux discloses epoxomicin, dihydroeponemycin, and PS-134, all of which comprise hydroxyl side chains, in addition to alkyl side chains and the amino acids of leucine, isoleucine, serine and phenylalanine. Reboud-Ravaux discloses Ritonavir which like PS-134, also has aromatic groups on the amino acid side chains, phenylalanine and valine. Reboud-Ravaux meets the limitation of claims 1 and 2 because the claims require only one of X0-X9 to be equal to one. Epoxomicin comprises 4 amino acids and therefore meets the limitation of claim 3.

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Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Hayashi et al (Biochemistry and Biophysics Research Communications, 1992, Vol. 182, pp. 939-946).

Hayashi et al disclose benxyloxycarbonyl-Leu-Leu-Leu-aldehyde (abstract, lines 12-13 and page 943, line 3) which meets the structural limitations of claim 1, wherein $X_0=0$, wherein X_1 , X_2 and X_3 each equal 1, wherein the bond is a peptide bond, and wherein the amino acids are capable of being modified at the alpha carbon; and the structural limitations of claim 2 wherein at least one of the integers of X_0 , X_1 , X_2 , X_4 , X_7 , X_8 and X_9 is equal to 1 and X_2 is chosen from a group including leucine.

Claims 1-3, 7-11 are rejected.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Crews et al (U.S. 6,831,099) disclose an Epoxomicin-biotin conjugate (figure 1)

Low et al (U.S. 5,108,921) teach the use of biotin and biotin-receptor binding ligands for the enhancement of transmembrane transport of exogenous molecules.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/

Primary Examiner, Art Unit 1643